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VIRUS RESEARCH IN HUNGARY

A Magyar Tudomany Tiz Eve
1945-1955 /Ten Years of
Science in Hungary 1945-1955/,
1955, Budapest, Pages 209-212

Gyorgy Ivanovics

In the period following the liberation virus research was conducted at the following institutes of medical science: the Virus Department of the OKI /Orszagos Kozegeszsegugyi Intezet -- National Institute of Public Health/, which was formed from the merger of the remnants of the old influenza laboratory and the sections which produce antityphoid and anti-rabies vaccine; the Institute of Microbiology of the University of Szeged; and at the dermatological clinic of the staff of the Pecs Medical School. The post-war research done at the Budapest Institute of Microbiology by Laszlo Berta came to an end with the untimely death of that young scientist. The present account does not include the results achieved by the institutes of veterinary science nor plant diseases.

In accordance with the investment plans of recent years the Virus Department of the OKI has been equipped for modern research in virology. The physical and morphological examinations which are necessitated by certain phases of virus research are now possible through the use of the departmental electron microscope and the analytical ultracentrifuge.

Combining the results achieved in virus research during the past 10 years into 3 rough categories, i.e.: 1. Introduction of virological research methods through adaptation of technical aspects to domestic circumstances and critical evaluation of the former. New methods, which are now characteristic of Hungarian virus research, were developed in the departmental laboratories during the course of these studies. Because of the simplicity, inexpensiveness and accuracy of these methods they undoubtedly will soon become recognized and applied on an international scale. 2. Virus research of a chiefly theoretical nature. 3. Practical investigations, aimed at identification of domestic diseases with unknown pathology, experimental research on the epidemiology of certain virus diseases, and the domestic adaptation of methods for the production of immunity against disease of a virus origin and the development of new methods for this purpose.

The microdilution method suggested by Takatsy is an important original work contributing to the methodology of domestic virus research. In this method a metal spatula is used instead of a pipette and scored glass slides are used instead of test tubes. This method has proved excellent in determination of the ability of influenza virus to agglutinate hemoglobin and in the titration of immunizing substances. This method is especially important in the field of conservation of laboratory work time and materials because it is approximately 10 times as effective as the methods in general use. Through his application and further perfection of the spatula dilution principle Horvath developed a new method for measurement of the degree of infectiveness of influenza virus. This new method greatly decreases laboratory work time and results in a great saving in materials, especially in the use of chick embryos. As a result of these savings the use of this method makes possible the performance of mass experiments. The micromethod of Horvath and Alfoldi exceeds the accuracy, and saves more time and materials than all the previously known phage-titration methods. This method also was developed during recent years.

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The measurement of the degree of infectiveness of viruses in micro tissue cultures also laid the foundation for cheap, mass virus experiments. Ivanovics and Hyde were the first, in 1935, to use a method for the determination of the degree of virulence of virus-containing substances without the use of large numbers of experimental animals. This method is based on the so-called cytopathogenic effect of viruses. This method was extended after World War II to the investigation in foreign countries of viruses which are difficult to study by other means, such as the poliomyelitis virus. Cserey-Pechany, Beladi, and Ivanovics used a method based on the principle of the cytopathogenic effect in investigation of the pathogenic agent of Aujeszky Disease. This method has been modified several times and perfected, and made the investigation of many theoretical questions possible. Beladi and Szollosy recently have experimented with the application of a method which has been in use in foreign countries during the past one or 2 years, consisting of the culture of independent colonies of viruses on a continuous section of tissue. Through adaptation of this tricky method isolated colonies of the Aujeszky virus now can be successfully cultured in Hungary. Systematic experiments have proved that changes in the allantois of chick embryos cannot be a positive indication of virus infection (Koch, Horvath, and Ivanovics). Attempts have been made by foreign researchers to use this method for the detection of very fine pathological changes in chick embryos.

With the use of an ultracentrifuge Takatsy developed a method for the production of influenza virus concentrates. Thus the prerequisites for the establishment of virus sedimentation constants have been attained in Hungary. Many excellent and valuable electron microscope photographs have been taken of influenza virus and rikettsia (Takatsy, Egyessy, and Szivessy), and of many, presently isolated and well-defined Pseudomonas aeruginosa bacteriophages (Lovas, Egyessy, and Alfoldi).

Domestic virus research has attained the following principal achievements in the field of problems with primarily theoretical significance. These include the study of the antigenic structure of influenza virus, which was made possible by the virus concentration method of Takatsy. The crossing-exhaustion method, which utilizes pure virus suspensions, added new data to the knowledge of the structure of influenza virus (Takatsy and Furesz). In the field of influenza virus research Farkas developed a blood adsorption method for the identification of this pathogenic group. Using the method he developed, Farkas compared many domestic and foreign strains of viruses. Red blood cells and other tissues contain the same connecting substance found in influenza, and related viruses. Ivanovics, Horvath and Szollosy studied the quantitative relationships of this substance. On the basis of their experiments utilizing the adsorption principle, the former obtained results with various species of animals which differ from previously accepted results. They also discovered that the lung epithelium of certain important experimental animals is able to bind viruses. These research studies uncovered several new facts concerning the pathogenic character of viruses. They also established the fact that viruses are bound on the inner surface of blood vessels. The above researchers then attempted to explain the familiar cardiovascular damage in influenza cases on the basis of this discovery. Berta, Molnar, and Garay conducted research on the effect of ultrasonic waves on influenza viruses, and Berta and Sinkovits investigated the problem of immunity to influenza, especially from the point of view of the importance of the reticuloendothelial system.

The study of professor Melczer on Behcet Disease also is within the field of virus research with theoretical importance. In the course of this study he was able to demonstrate the presence of mineral bodies

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and fossilized insects in mucus afta scrapings. On the basis of fluorescent microscopic studies Melczer also discovered that various viruses are stained differently by primulin. Melczer considers this method to be suitable for the positive comparison of viruses, also.

It also may be mentioned that Penter and Beladi have succeeded in culturing the pathogenic agent of Czechoslovakian tick-encephalitis in a tissue culture.

Virus propagation and the mechanics of this process is one of the central research tasks of the Szeged Institute of Microbiology. For his candidate's dissertation Alfoldi amassed a great deal of experimental data in his study of the lysogenesis of Ps. aeruginosa. Ivanovics and Alfoldi detected a new, lethal biosynthesis in certain strains of B. megatherium. The product of this pathological synthesis, which they named megacin, apparently is an incomplete phage. The culturing of the virus of Aujeszky's disease in tissue cultures has yielded new data on the cyclical development of viruses (Agraham, Koch, and Ivanovics). Ivanovics, Beladi and Szollosy have demonstrated that the Aujeszky disease virus can change, or can be acclimated to the tissue of certain species of animals.

Hungarian virus researchers have been able to cite many achievements during the past 10 years in connection with the pathogenesis of domestic infectious diseases. During the influenza epidemic of 1949 Farkas and Takatsy discovered for the first time the presence of sub-type A and B virus strains in Hungary. During the epidemic of 1950-1951 Domok, Farkas, and Gal isolated various influenza species, and obtained valuable epidemiological data in the study of the serum of convalescents. Influenza species were isolated and their antigen structure carefully studied by Szollosy, Abraham, and Alfoldi during the 1952 influenza epidemic at Szeged, and in January 1954 by Horvath and Balazs. All of the latter species proved to be of subtype A. It is a noteworthy fact that the recently discovered influenza C virus was first isolated on the European continent in Hungary (Farkas and Domok).

The virus of fowl disease (Newcastle's disease) occasionally causes mild illness in humans. The virus of the so-called oculoglandular disease (Radnot) was first isolated on the European continent in Hungary (Sinkovits). Several species of mumps virus also have been isolated and studied in Hungary (Takatsy and Szafir).

The investigation of contagious diseases affecting the nervous system constituted an important problem of virus research in Hungary. These investigations also provide insight into the pathology of the large number of serous meningitis diseases. The lymphocytic coriomeningitis virus strains also were isolated first in Central Europe in individual sporadic cases which occurred in the Szeged vicinity. The isolation of the identical virus from the organs of mice found in the vicinity of the patients afflicted with the disease also gave some indication of its origin (Ivanovics, Koch, and Pinter).

The virus later was found by other researchers (Molnar and Domok) in sick persons in other parts of the country. These cases were diagnosed retrospectively through serological tests (Farkas and Domok). The first domestic case of the recently discovered Coxsackie-virus infection, which has an extremely varied clinical course, was diagnosed through examination of specimens taken from a patient at Szeged. In the study of an epidemic center Pinter and Balazs isolated many species, which were compared with foreign species and the domestic strain was identified. At Budapest Domok also has isolated and studied many Coxsackie species.

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Fornosi and Molnar have done some exceptionally important pathogenetic and epidemiological research at the Tatabanya encephalitis epidemic center. These two researchers established the origin of tick-encephalitis by isolating and identifying the virus from a mass of ticks. Neutralization tests performed with the isolated species were a valuable aid to the clarification of the pathogenesis of this disease which has had numerous incident cases for many years in the epidemic center.

Research on poliomyelitis also has been undertaken in recent years. Neutralization experiments were performed with the Lansing mouse-pathogenic species on the blood serum of individuals of the Szeged region who have never been afflicted with infantile paralysis. It was established that this virus often causes latent infection in Hungary. The recovery from this latent infection is in large part identical with conditions described in western states (Pinter).

Polio research is being conducted utilizing human embryo tissue at Szeged (Pinter and Ravnay) and at the OKI (Foldes). Neutralization tests have been performed and some virus species have been isolated from the stool of patients at both research centers. Because of a lack of typical sera, however, the latter have not been identified.

In connection with immunization against virus diseases it may be mentioned that Fornosi and Ujhelyi have obtained very favorable results with the Hempt vaccine, which has been successfully adapted and produced domestically. Thus lysis-prevention, or therapy may be conducted in Hungary in a decentralized manner. Vaccination against Aujeszky's disease may be performed under laboratory conditions (Beladi and Ivanovics). This disease may still be of importance in veterinary science. Immunization against this discase previously was impossible.

In the field of rikettsia research, the occurrence of Q-fever in Hungary has been proved. This disease is not uncommon among Budapest slaughterhouse workers (Farkas, Gero, and Takatsy). Brill's disease, which is observed as a relapse of typhoid fever has been detected in Hungary in recent years and has been verified by laboratory examinations (Domok, Farkas, Furesz, and Mihalyfi).

The phage classification of entereal bacteria has been assimilated in recent years by Eorsy. Eorsy drew attention to the fact that the bacteriophage of dyspepsiacoli frequently is found in the stool during the course of the disease. According to Eorsy both the bacterium and its phage are equally responsible for the clinical picture of the disease.

In summary: during the past 10 years Hungarian virus research has achieved notable results in the field of current, actual problems. Hungarian virus research has reached and surpassed the average international level. The results of Hungarian virus research not only have furthered the development of Hungary's public health, but may rely upon international recognition for its achievements. This is even more noteworthy because Hungarian virus research began from meager straights following Liberation, and within 10 short years has developed into a broad, many-tiered branch of science which is based on many of its own research methods.

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